REMARKS

Reconsideration is requested.

Claim 64, directed to combinations of probes, has been added. Support for the amended claims may be found throughout the specification. No new matter has been added. No new matter has been added. Claims 41-64 are pending.

The Examiners interview with the undersigned on March 13, 2003, is acknowledged, with appreciation. The Interview Summary is an accurate summary of the issues discussed. While claim 53 has been withdrawn from consideration, the Examiners appeared to suggest that the claim may be rejoined an allowed with claim 43, from which claim 53 depends, if claim 43 is found allowable.

Attached a Request for a 3 month suspension of action to allow the applicants an opportunity to further consider the Examiners' position expressed during the interview. The fee required by Rule 103 is also attached.

The Section 112, second paragraph rejection of claims 41-52 and 54-63 is obviated by the above amendments. Reconsideration and withdrawal of the Section 112, second paragraph rejection of claims 41-52 and 54-63 is requested.

The following abbreviation for the cited art will be used in the following, for conservation of space and paper:

D1 - Botelho (Yeast, Vol 10, pp 709-717, 1994);

D2 - Hogan (U.S. Patent No. 5,595,874);

D3 - Williams (J. Clinc Path, Vol 49, No. 1, pp 1423-1428);

D4 - Lin (Deposit Accession No. U10987);

D5 - Lin (J. Clin Micro, Vol 33, No. 7, pp 1815-1821, July 1995);

D6 - Messner (Deposit Accession No. U09325);

D7 - Williams (Deposit Accession No. L47108);

D8 - Lott (U.S. Patent No. 6,242,178);

D9 - Fujita (J. Clin Micro, Vol 33, No. 4, pp 962-967, April 1995); and

D10 - Jordan (U.S. Patent No. 6,017,699).

The Examiner has made the following Section 103 rejections of the indication claims:

Rejection ¶ No. in Paper No. 24	Claims	Reference Combination
7	41-43, 45 and 47	D1 and D2
8	41-45, 47 and 49	D3 and D2
9	41-48 and 50	D3 and (D4 or D5 or D6 or D7) and D2
10	41-43 and 51	D8 and D2
11	52	D1, D2 and D9
12	52	D3, D2 and D9
13	52	D3 and (D4 or D5 or D6 or D7) and D2 and D9
14	52	D8 and D2 and D9
15	54, 56 and 63	D1, D2 and D10
16	54-56, 58, 60 and 63	D3, D2 and D10

Rejection ¶ No. in Paper No. 24	Claims	Reference Combination
17	54-59, 61 and 63	D3 and (D4 or D5 or D6 or D7) and D2 and D10
18	54-55, 62 and 63	D8 and D2 and D10

The applicants believe the Examiner has appreciated that none of the cited art teaches the presently claimed probes or uses of the same.

The applicants submit that the only cited references which disclose probes of a nature of the presently claims invention are references D1 and D8. Any rejection based on art not including these references would therefore be so remote as to provide, at best, only a suggestion that it would have been obvious to try to make the presently claimed invention. The applicants do not even believe the cited art provide such a remote suggestion. In any event, rejections based on art which does not include cited references D1 or D8 are not believed to provide a *prima facie* case of obviousness as the combination of art fails to reasonably suggest the presently claimed invention.

The rejections of the Examiner's numbered ¶¶ 8, 9, 12, 13, 16 and 17 therefore should be withdrawn.

As for the rejections of the Examiner's numbered ¶¶ 7, 11 and 15, which rely on D1, the applicants traverse the rejections. Reconsideration and withdrawal of the rejections are requested for the following reasons.

D1 teaches three "distinct regions with sufficient sequence divergence to make them suitable as specific target sites for the identification of *C.* albican." See, Abstract (emphasis added). The authors of D1 therefore conducted detailed analysis of species-

specific probes and identified three C. *albicans* probes, i.e., ANAB1 and ANAB2 and ANAB3, two of which are ITS2 sequences (ANAB2 and ANAB3) and one of which is an ITS1 sequence (ANAB1). See, Figure 2 of D1. The probes of the presently claimed invention are not specifically taught by D1. Moreover, the sequences of the presently claimed invention do not include an ITS2 *C. albicans* probe. Reading D1 therefore, one of ordinary skill in the art wishing to make the presently claimed invention would have required motivation to believe that the authors of D1 had not identified distinct regions suitable as specific target sites for identification of *C. albicans*. Such a conclusion however would have been contrary to the teaching of D1, as quoted above. The further identification of *C. albicans* specific probes, as presently claimed, therefore would have been contrary to the teachings of D1. The presently claimed invention would not have been obvious in view of D1 and the cited secondary references of the Examiner's numbered paragraphs 7, 11 and 15 fail to cure the deficiencies of D1, as noted above.

For completeness, the applicants note that the *C. albican* ITS1 sequence is as follows (wherein the ANAB1 probe is shown in bold, strike-through type and the presently claims SEQ ID NOs:2 and 3 are shown in italics and lower case type, respectively):

Candida albicans ITS1

CTGATTTGCTTAATTGCACCACATGTGTTTTTCCGCCAGAGGTCTAAACTTACAACCAATTTTTT*TATCAACT*

*tgtcacaccaga*ttatt~~a~~ctAATAGTCAAA

With regard to the rejections of the Examiner's numbered paragraphs 10, 14 and 18 and the combinations of art which rely on D8, the applicants submit the reference fails to teach or suggest that a shorter sequence of the *Candida dubliniensis* SEQ ID NO:35 of D8, such as the applicants' claimed SEQ ID NO:12, would be useful. The applicants submit that the cited secondary art fails to cure this deficiency and the rejections based on D8 should be withdraw.

For completeness, the applicants note that the Examiner is understood to believe that the claimed nucleic acid sequences and methods of using these novel nucleic acid sequences would have been obvious based on teachings in the cited art relating to methods of designing oligonucleotide probes. At best, the Examiner's comments and cited art only provide a basis for a possible suggestion that it may have been obvious to try to make the presently claimed invention. A *prima facie* case of obviousness, under 35 U.S.C. § 103, however requires more than a possible suggestion that it may have been obvious to have tried to make and/or use the presently claimed invention.

The Examiner is urged to appreciate that the claims are not directed to methods of designing oligonucleotide probes, but methods of using specific nucleic acid sequences, which are novel chemical entities, in structural terms, and also a method for detecting *Candida* species using these specific nucleic acids sequences.

A general motivation to search for some probes in a gene does not establish a *prima facie* case of obviousness of the claimed nucleic acid sequences, or methods of using the same, which have been obtained as a result of a specific discovery, such as

the applicants' discovery of the presently claimed nucleic acid sequences which are functional under the same hybridisation conditions, for use in detection of *Candida* species. Whether the claimed methods specifically require or state that the same hybridisation conditions may be used is not believed to be critical to the patentability over the cited art as the cited art fails to teach or suggest the specific nucleic acid sequences of the present claims. The previous remarks relating to the same were submitted to stress an unobvious property or advantage of the presently claimed nucleic acid sequences which are inherent to the nucleic acid sequences.

The nucleic acid sequences and/or probes disclosed in the cited art have been recognized to be different (i.e., not anticipatory) of the presently recited and disclosed nucleic acid sequences. The Examiner is urged to appreciate that the court has held that some motivation to select the claimed species or subgenus must be taught by the cited prior art, to establish a *prima facie* case of obviousness. See, In re Deuel. 34 USPQ2d 1215 and MPEP § 2144.08 (page 2100-139, August 2001) ("No particular one of these DNAs can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared."); In re Baird 29 USPQ2d at 1552; and In re Bell, 26 USPQ2d at 1531 ("Absent anything in the cited prior art suggesting which of the 10^{36} possible sequences suggested by Rinderknecht corresponds to the IGF gene, the PTO has not met its burden of establishing that the prior art would have suggested the claimed sequences.").

The Examiner is also urged to appreciate that the court has held that in making

an obviousness determination, the PTO should consider the number of variables which must be selected or modified, and the nature and significance of the differences between the prior art and the claimed invention. See, e.g., In re Jones,21 USPQ2d 1941, 1943 (Fed. Cir. 1992) and MPEP § 2144.08, page 2100-140, August 2001. As noted above, the presently claimed invention provides a significant advantage over the cited art in allowing hybridisation under the same conditions.

In an attempt to make up for the deficiency of D1 and D8, as well as the other cited art, the Examiner cites, as a secondary reference, for example, Hogan.

The Examiner alleges that Hogan teaches a method for the selection of specific probes and thus, provides motivation to obtain the probes of the presently claimed nucleic acid sequences. The applicants respectfully submit however that, contrary to the Examiner' s assertions, the teachings of Hogan, and other related secondary references, are generic, and fail to provide any guidance to specifically design the sequences of the presently claimed invention.

The Examiner is urged to review MPEP § 2144.09 (page 2100-148, August 2001), for example, which states as follows:

> "In the biotechnology arts, the existence of a general method of gene cloning in the prior art is not sufficient, without more, to render obvious a particular cDNA molecule. *In re Deuel*, ... 34 USPQ2d 1210, 1215 (Fed. Cir. 1995) ("[T]he existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question of whether the specific molecules themselves would have been obvious, in the absence of other prior art that suggests the claimed DNAs."); *In re Bell*, ... 26 USPQ2d 1529, 1532 (Fed. Cir. 1993)."

The passage in Hogan cited by the Examiner[1] is a general teaching of how to make a probe which would not have led one of ordinary skill in the art, even in combination with the other cited art, to have made and/or used the specific novel nucleic acid sequences of the presently claimed invention.

The Examiner has not explained how the cited text from Hogan would have actually provided motivation to one of ordinary skill in the art to have specifically identified and selected the specific nucleic acid sequences of the presently claimed invention from a myriad of possible sequences taught by the Examiner's multitude of references.

At best, the cited combination of art would have perhaps made it obvious to try to make the presently claimed invention. The Examiner has not established a *prima facie*

---

[1] "Once the variable regions are identified, the sequences are aligned to reveal areas of maximum homology or 'match'. At this point, the sequences are examined to identify potential probe regions. Two important objectives in designing a probe are to maximize homology to the target sequence(s) (greater than 90% homology is recommended) and to minimize homology to non-target sequence(s) (less than 90% homology to non-targets is recommended). We have identified the following useful guidelines for designing probes with the desired characteristics.

First, probes should be positioned so as to minimize the stability of the probe:nontarget nucleic acid hybrid. This may be accomplished by minimizing the length of perfect complementarity to non-target organisms, avoiding G and C rich regions of homology to non-target sequences, and by positioning the probe to span as many destabilizing mismatches as possible (for example, dG:rU base pairs are less destabilizing than some others). Second, the stability of the probe:target nucleic acid hybrid should be maximized. This may be accomplished by avoiding long A and T rich sequences, by terminating the hybrids with G:C base pairs and by designing the probe with an appropriate Tm. The beginning and end points of the probe should be chosen so that the length and %G and %C result in a Tm about 2-10^{0}C higher than the temperature at which the final assay will be performed. The importance and effect of various assay conditions will be explained further herein. Third, regions of the rRNA which are known to form strong structures inhibitory to hybridization are less preferred. Finally, probes with extensive self complementarity should be avoided."

case of obviousness.

Withdrawal of the Section 103 rejections is requested.

The claims are submitted to be patentable over the cited art and a Notice of Allowance is requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____

B. J. Sadoff
Reg. No. **36,663**

BJS
1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100